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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/695,744	10/30/2003	Patrizia Paterlini-Brechot	2121-0178P	7652

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EXAMINER

MYERS, CARLA J

ART UNIT	PAPER NUMBER
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1634

MAIL DATE	DELIVERY MODE
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12/20/2006

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

<p align="center">Advisory Action Before the Filing of an Appeal Brief</p>	Application No. 10/695,744	Applicant(s) PATERLINI-BRECHOT, PATRIZIA	
	Examiner Carla Myers	Art Unit 1634	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 November 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 28 November 2006. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
 (b) ☐ They raise the issue of new matter (see NOTE below);
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
 5. ☐ Applicant's reply has overcome the following rejection(s): _____.
 6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
 7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
 The status of the claim(s) is (or will be) as follows:
 Claim(s) allowed: _____.
 Claim(s) objected to: _____.
 Claim(s) rejected: 1,4,5,9-18 and 20-25.
 Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attachment.
 12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____.
 13. ☐ Other: _____.

Attachment to Advisory

Continuation of Box 11: The request for reconsideration has been considered but does not place the application in condition for allowance. In the response, Applicants traverse the previous rejections of the claims under 35 U.S.C. 103. In summary, on pages 8-15 of the response, Applicants present their interpretation of the teachings of Kalionis. On pages 16-18, Applicants present their interpretation of the teachings of Vona.

Applicants state that in the method of Kalionis, the immunostaining step is performed after the cells are collected, whereas in the presently claimed method, the immunostaining step is performed before the step of cell collection. This argument has been fully considered but is not persuasive. Applicants response separately addresses the teachings of Kallionis and Vona. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Kalionis in fact teaches filtering a sample of maternal blood through a filter, then analyzing the cells to confirm their identity as being of fetal origin, subsequently analyzing the individual cells by in situ hybridization and immunostaining to demonstrate that the cells are fetal cells and analyzing the individual cells identified as being fetal cells for the presence of a genetic anomaly or to determine the sex of the fetal cell. Vona teaches methods for isolating rare cells from blood wherein the methods comprise passing a blood sample through a filter to retain target cells according to size, analyzing the cells retained on the filter to confirm their identity, using microdissection with the aid of a laser to individually collect

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the isolated cells retained on the filter into a tube in order to obtain a single collected cell (see pages 58-60), and then amplifying the nucleic acids from the isolated cells and then detecting the amplified nucleic acids. Thereby, Vona teaches a method wherein the immunostaining step for determining the identity of a cell is performed prior to the step of microdissection (i.e., the step of collecting an identified cell).

The response argues that Kalionis does not teach a method of dual in situ hybridization using both probes that are specific for trophoblast mRNA and probes that are "specific for human chromosomes" (i.e., a probe that could be used for prenatal diagnosis). However, the Office action does not state that Kalionis teaches a method of dual in situ hybridization. Rather, the Office action states that Kalionis teaches a method in which cells are first analyzed by in situ hybridization to demonstrate that the cells are fetal cells (col. 10 and 19) and then the individual fetal cells are analyzed to detect a genetic anomaly or to determine the sex of the fetal cells.

Applicants state that the "Kalionis reference does neither disclose nor suggest a method, which would comprise a step that would resemble step b) of the claimed method." Again, this argument is not persuasive because the present rejection is not based on the teachings of Kalionis alone. Rather, the present rejection is based on the combined teachings of Kalionis and Vona.

The response at page 15 states that "the claimed method is only very distantly related to the Kalionis method." This argument is not persuasive and does not accurately characterize the teachings of Kalionis. Kalionis is in fact highly analogous art to the claimed invention. The method of Kalionis differs from the claimed invention only

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in that Kalionis does not teach collecting individual fetal cells by microdissection, followed by amplification and detection of the nucleic acids present in the collected fetal cells. However, Vona was cited for its teachings of collecting individual fetal cells (trophoblast cells) by microdissection, amplifying the nucleic acids present in the individual cells and further detecting the amplified nucleic acids.

Applicants argue that the Vona reference does not disclose a step that would resemble step b) of the claimed method, wherein cells retained on a filter are immunologically or cytologically analyzed prior to collecting an appropriate cell. This argument has been fully considered but is not persuasive. Vona does in fact teach a method comprising filtering a biological sample, cytologically analyzing the cells retained on the filter, and then performing the microdissection technique to isolate individual identified cells (see page 58, col. 2; page 59, col. 2).

The response argues that Vona does not disclose a method wherein the amplification step would comprise the demonstration of two clinical features. This argument is also not persuasive because it is based on the teachings of Vona alone, whereas the present rejection is based on the combined teachings of Kalionis and Vona. Kalionis teaches that the individual cells are subsequently analyzed to both confirm that the cells are of fetal origin and to determine the sex of the cell or to detect a genetic abnormality. Thereby, when taken collectively, the combined references would have suggested a method in which the amplified nucleic acids were analyzed to both confirm the fetal origin of the cells and to carry out prenatal diagnosis.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Carla Myers

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CARLA J. MYERS
PRIMARY EXAMINER